PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SAMA, Daniele et al.
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 20.03.2001
Applicant's or agent's file reference HF 2112/061/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/07222	27/07/2000	04/08/1999

Applicant
NICOX S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel.+49 89 2399-8031

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 May 2001 (03.05.01)	
International application No. PCT/EP00/07222	**Applicant's or agent's file reference** HF 2112/061/PCT
International filing date (day/month/year) 27 July 2000 (27.07.00)	**Priority date** (day/month/year) 04 August 1999 (04.08.99)
Applicant BENEDINI, Francesca et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 January 2001 (26.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HF 2112/061/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/07222	27/07/2000	04/08/1999
International Patent Classification (IPC) or national classification and IPC C07C203/04		
Applicant NICOX S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/01/2001	20.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cooper, S Telephone No. +49 89 2399 8323

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/07222

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-8 as originally filed

Claims, No.:

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
see separate sheet

Section V.

1). The application relates to the preparation of nitroxyalkyl esters of (S)-naproxen from the acyl halide of (S)-naproxen and the corresponding nitroxyalkanol. Whilst the process is in particular characterised by the use of an inorganic base for the esterification, no example could be located in the available prior art in which an acid halide of (S)-naproxen and a nitroxyalkanol were used as reaction partners. The present process is therefore novel.

2). The invention is based on the finding that where the acid halide of (S)-naproxen is reacted with a specified nitroxyalkanol, less racemisation of the naproxen occurs when an inorganic base is used than when an organic base is used, which effect is demonstrated in the examples and comparative examples 7-9.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HF 2112/061/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/07222	27/07/2000	04/08/1999
International Patent Classification (IPC) or national classification and IPC C07C203/04		
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26/01/2001	20.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cooper, S Telephone No. +49 89 2399 8323

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/07222

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
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6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
see separate sheet

Section V.

1). The application relates to the preparation of nitroxyalkyl esters of (S)-naproxen from the acyl halide of (S)-naproxen and the corresponding nitroxyalkanol. Whilst the process is in particular characterised by the use of an inorganic base for the esterification, no example could be located in the available prior art in which an acid halide of (S)-naproxen and a nitroxyalkanol were used as reaction partners. The present process is therefore novel.

2). The invention is based on the finding that where the acid halide of (S)-naproxen is reacted with a specified nitroxyalkanol, less racemisation of the naproxen occurs when an inorganic base is used than when an organic base is used, which effect is demonstrated in the examples and comparative examples 7-9.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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WO 01/10814 A1

(54) Title: PROCESS FOR THE PREPARATION OF NAPROXENE NITROXYALKYLESTERS

(57) Abstract: A process for obtaining nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO_2, wherein Y is a C_2-C_{20} alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorganic base.

PROCESS FOR THE PREPARATION OF NAPROXENE NITROXYALKYLESTERS

* * * * * *

The present invention relates to a new method for preparing nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (naproxene) having an enantiomeric excess of the (S) form higher than or equal to 97%, preferably higher than or equal to 98%, combined with high yields, higher than 75-80%, preferably higher than 85%.

It is well known in the prior art that the enantiomeric form (S) is the active form from the pharmacological point of view of the above mentioned product.

In the prior art synthesis methods of nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid, are known. In the patent application WO 98/25,918, a synthesis method of naproxene nitroxyalkyl esters containing in the alkyl chain a saturated C_3-C_8 cycloalkyl residue, is described. In said process the acid or one of its functional derivatives, for example, chloride or anhydride, is reacted, in an inert organic solvent, with a nitroalkanol containing a cycloalkyl residue as above defined. The reaction takes place in the presence of an organic nitrogenated base, such as for example 4-dimethyl aminopyridine, morpholine, N-methyl morpholine or triethylamine. Tests carried out by the Applicant have shown

that this process of the prior art does not allow to obtain naproxene nitroxyalkylesters having an enantiomeric excess in the range of 55-80%, only with a specific organic base, 4-N,N-dimethylamino pyridine, 94% is obtained.

The need was therefore felt to obtain naproxene nitroxyalkylesters having an higher enantiomeric excess, at least of 97%, preferably equal to or higher than 98%.

An object of the present invention is a process to obtain nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 97%, preferably higher than or equal to 98%, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acylic residue of said acid, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO_2, wherein Y has one of the following meanings:

- a linear or optionally branched C_1-C_{20}, preferably C_2-C_5, alkylene;
- a cycloalkylene with ring from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, said cycloalkylene optionally can be substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene;
- an aromatic residue with ring having 5 or 6 carbon atoms,

said aromatic residue optionally can be substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene, or a -COOH group;

- $-(T)_p-(CH(CH_2ONO_2)-CH_2O)_{nf'}-(T)-$,

$-(T)_p-(CH_2-CH(ONO_2)-CH_2O)_{nf'}-(T)-$,

T being alkylene as above dfeined and p an integer equal to zero or one, alkylene having the above mentioned meaning, nf' is an integer from 1 to 6, preferably from 1 to 4; in the presence of an inorganic base, to give the corresponding nitroxyalkylester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula $A-O-Y-ONO_2$, wherein A and Y are as above defined.

Y can also be a combination of two or more of the mentioned group.

The aliphatic nitroxyalcohol amount on molar basis is in the range 1-2, preferably 1.2-1.5, with respect to that of the acid halide.

With inorganic bases hydroxides, oxides, carbonates and bicarbonates, silicates, aluminosilicates of the alkaline and alkaline-earth metals, or hydroxides, oxides, carbonates and bicarbonates of metals belonging to the group IIB, preferably zinc, or to groups IIIa or IVa, preferably tin, are meant.

The inorganic base amount is in molar ratio with the acid

halide amount generally in the range 1-2, preferably 1.2-1.5.

With inert organic solvent according to the present invention aromatic hydrocarbons are meant, such as for example toluene and xylene, chlorinated or fluorinated organic solvents, for example methylene chloride, chlorobenzene, aliphatic esters for example C_1-C_4 acids esters with C_1-C_5 alcohols such as for example ethyl acetate and butyl acetate, etc.

The solvent amount is not critical and generally from 1 to 10 volumes of solvent are used, preferabaly from 2 to 5 volumes based on the acid halide weight.

The reaction is carried out at a temperature in the range -20°C and 50°C, preferably 0°C and 20°C.

The nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid are recovered at the end of the reaction, after addition of water to the organic phase, separation of the phases and solvent evaporation. If necessary, a further purification can be carried out by chromatography on silica gel column in order to increase the product titre.

Alternatively, the compound can also be purified by crystallization from a suitable solvent.

Aliphatic nitroxyalcohols can be prepared according to the known methods in the prior art. See for example Gazzetta Chim. It. 1987, 117, 173 and WO 98/25,918.

The Applicant has found that surprisingly by the use of

inorganic bases it is possible to improve the enantiomeric excess of naproxene nitroxyalkylesters with respect to the prior art methods, which use, as seen, organic bases, with high yields as above mentioned.

The following examples have the purpose to illustrate the invention and they are not to be intended as limitative thereof.

EXAMPLE 1 (comparative)

Preparation of 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid according to WO 98/25918

A mixture of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (0.32 g, 1.4 mmoles), 4-N,N-dimethylamino pyridine (16 mg, 0.13 mmoles), 4-nitroxybutan-1-ol (0.34 g, 2.5 mmoles) in dichloromethane (6 ml) at a temperature in the range 0°C-5°C is added, under stirring, to a solution of N,N'-dicyclohexylcarbodiimide (0.29 g, 1.4 mmoles) in dichloromethane (6 ml). The mixture is left under stirring at the same temperature for 3 hours and then dried by solvent evaporation under vacuum. The residue is purified by chromatography on silica gel column (eluent dichloromethane) to give the 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (0.41 g, 1.19 mmoles), yield 85%) in the form of an oil. HPLC purity: 98%.

^{1}H NMR($CDCl_3$) δ (ppm): 1.59 (d, 3H, J=7.5 Hz); 1.65 (m, 4H); 3.85 (q, 1H, J=7.5 Hz); 3.91 (m, 2H); 4.10 (m, 2H); 7.1-7.7

(m, aromatic, 8H).

Enantiomeric excess: 94%.

EXAMPLE 2

To a solution of 4-nitroxybutan-1-ol (2.0 g; 14.8 mmoles) in dichloromethane (20 ml), cooled at 0°C-5°C, potassium carbonate (3.21 g, 23.2 mmoles) is added under stirring.

To the mixture a solution of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid chloride (3.86 g, 15.5 mmoles; enantiomeric excess 98%) in dichloromethane (22 ml) is added, maintaining the temperature in the range 10°C-15°C. When the addition is over the temperature is increased and maintained for 10 hours at a value in the range 15°C-20°C and then the solution is filtered. The solvent is evaporated under vacuum. The residue is purified by chromatography on silica gel column (eluent dichloromethane) to give the 4-nitroxybutyl ester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (4.4 g, 12.6 mmoles, yield 85%) in the form of an oil. HPLC purity: 99%.

^{1}H NMR($CDCl_3$) δ (ppm): 1.59 (d, 3H, J=7.5 Hz); 1.65 (m, 4H); 3.85 (q, 1H, J=7.5 Hz); 3.91 (m, 2H); 4.10 (m, 2H); 7.1-7.7 (m, aromatic, 8H).

Enantiomeric excess: 98%.

EXAMPLE 3

Example 2 is repeated using toluene as solvent. The nitroxyester yield is 76%, the (HPLC) purity > 99%. The enatiomeric excess is equal to 98%.

EXAMPLE 4

Example 2 is repeated but using as a base calcium carbonate. 4.6 g, equal to 13.3 mmoles of nitroxyester (yield 90%) are obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 5

Example 2 is repeated but using as a base calcium alumino-silicate. 4.6 g, equal to 13.3 mmoles of nitroxyester (yield 90%) are obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 6

To a solution of 4-nitroxybutan-1-ol (2.0 g; 14.8 mmoles) in dichloromethane (20 ml), cooled at a temperature in the range 0°C-5°C, potassium carbonate (3.21 g, 23.2 mmoles) is added under stirring.

To the mixture a solution of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid chloride (3.86 g, 15.5 mmoles, enantiomeric excess 98%) in dichloromethane (22 ml) is added, maintaining the temperature in the range 10°C-15°C. When the addition is over, the temperature is increased to a value in the range 15°C-20°C for 10 hours and then the solution is filtered. Water (1 ml) and N,N-dimethylformamide (2 ml) are added to the solution and left under stirring at room temperature for 3 hours. At the end the organic phase is separated, washed with water and filtered through a potassium carbonate panel. The solvent is evaporated under vacuum and 4.1 g, equivalent to 11.8 mmoles of ester (yield 80%) in the form of an oil, are

obtained, HPLC purity >99%, enantiomeric excess 98%.

EXAMPLE 7 (comparative)

Example 2 is repeated but using as a base triethylamine. The obtained mixture after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 80%.

EXAMPLE 8 (comparative)

Example 2 is repeated but using as a base diisopropylethylamine. The mixture obtained after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 76%.

EXAMPLE 9 (comparative)

Example 2 is repeated but using as a base N-methylmorpholine. The mixture obtained after the reaction is analyzed to evaluate the enantiomeric excess, which results equal to 56%.

CLAIMS

1. A process for obtaining nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess higher than or equal to 97%, preferably higher than or equal to 98%, characterized in that an halide of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula A-Hal, wherein A is the acyl residue of the acid, is let react in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO_2, wherein Y has one of the following meanings:

- a linear or optionally branched C_1-C_{20}, preferably C_2-C_5, alkylene, or
- a cycloalkylene with ring from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, said cycloalkylene optionally substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene;
- an aromatic residue with ring having 5 or 6 carbon atoms, said aromatic residue optionally substituted with one or two alkylenes as above defined, and/or with one or more alkyl radicals having in the chain a number of carbon atoms as above defined for alkylene, or a -COOH group;

- $-(T)_p-(CH(CH_2ONO_2)-CH_2O)_{nf'}-(T)-$,

$-(T)_p-(CH_2-CH(ONO_2)-CH_2O)_{nf'}-(T)-$,

T being alkylene as above defined and p an integer equal to zero or one, alkylene having the above mentioned meanaing, nf' is an integer from 1 to 6, preferably from 1 to 4;

in the presence of an inorganic base, to give the corresponding nitroxyalkylester of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid of formula $A-O-Y-ONO_2$, wherein A and Y are as above defined.

2. A process according to claim 1, wherein the aliphatic nitroxyalcohol amount on molar basis is in the range 1-2, preferably 1.2-1.5, with respect to that of the acid halide.

3. A process according to claims 1 and 2, wherein the inorganic bases are hydroxides, oxides, carbonates and bicarbonates, silicates, aluminosilicates of the alkaline and alkaline-earth metals, or hydroxides, oxides, carbonates and bicarbonates of metals belonging to the group IIB, preferably zinc, or to groups IIIa or IVa, preferably tin.

4. A process according to claims 1-3, wherein the inorganic base amount is in molar ratio with the acid halide amount in the range 1-2, preferably 1.2-1.5.

5. A process according to claims 1-4, wherein the reaction is carried out at a temperature in the range -20°C and 50°C, preferably 0°C and 20°C.

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/EP 00/07222

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 30641 A (NICOX LTD) 16 November 1995 (1995-11-16) examples 1C,1H ---	1-5
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonnevalle, E

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Inte. onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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